Bevacizumab Alone or in Combination with Irinotecan in Recurrent WHO Grade II and Grade III Gliomas

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Abstract: Background: The repertoire of salvage regimens for patients with WHO grade II and III gliomas recurring or progressing after surgery, radiotherapy and temozolomide chemotherapy is limited. Based on promising response and progression-free survival (PFS) data in recurrent glioblastoma, the use of bevacizumab (BEV) has been extended to recurrent grade II/III gliomas. Methods: We retrospectively assessed the safety and efficacy of BEV alone or combined with irinotecan in 39 patients with recurrent grade II/III gliomas. Results: Both BEV monotherapy and its combination with irinotecan were well tolerated. Response rates were 26% as monotherapy and 33% in combination using Macdonald and RANO criteria. The median PFS was 4.2 months and the PFS rate at 6 months 29% for BEV alone, and 4.7 months and 42% for the combination. The median overall survival was 14.8 months for BEV monotherapy and 8.1 months for the combination. Outcome after failure of BEV was better when patients continued BEV beyond progression. Conclusion: BEV has limited activity in recurrent grade II/III gliomas. The additional value of irinotecan remains questionable. Prospective studies with BEV-free control groups are required to better define the role of BEV among the limited options in patients with recurrent grade II/III gliomas.

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Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas

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Short title: Bevacizumab and irinotecan in grade II and grade III gliomas

Keywords: bevacizumab, glioma, irinotecan, angiogenesis

Abstract

Background: The repertoire of salvage regimens for patients with WHO grade II and III gliomas recurring or progressing after surgery, radiotherapy and temozolomide chemotherapy, is limited. Based on promising response and progression-free survival (PFS) data in recurrent glioblastoma, the use of bevacizumab (BEV) has been extended to recurrent grade II/III gliomas.

Methods: We retrospectively assessed the safety and efficacy of BEV alone or combined with irinotecan in 39 patients with recurrent grade II/III gliomas.

Results: Both BEV monotherapy and its combination with irinotecan were well tolerated. Response rates were 26% as monotherapy and 33% in combination using Macdonald and RANO criteria. Median PFS was 4.2 months, and the PFS rate at 6 months (PFS-6) 29%, for BEV alone, and 4.7 months and 42% for the combination. The median overall survival (OS) was 14.8 months for BEV monotherapy and 8.1 months for the combination. Outcome after failure of BEV was better when patients continued BEV beyond progression.

Conclusion: BEV has limited activity in recurrent grade II/III gliomas. The additional value of irinotecan remains questionable. Prospective studies with BEV-free control groups are required to better define the role of BEV among the limited options in patients with recurrent grade II/III gliomas.

Background

WHO grade II and III gliomas comprise astrocytic, oligodendroglial and oligoastrocytic tumors and represent a heterogeneous group of tumors regarding natural course, benefit from treatment, and prognosis. Surgery, radiotherapy and chemotherapy have a role in the treatment of WHO grade II gliomas, but their sequence and timing remain controversial [1]. Multimodal therapy including surgery followed by radiotherapy or temozolomide chemotherapy represents the current standard of care in most countries [2]. At recurrence or failure of these standard therapeutic options, the repertoire of salvage regimens is limited. Phase II chemotherapy trials in patients with recurrent anaplastic gliomas in the pre-temozolomide era showed response rates in the range of 14% and progression-free survival (PFS) rates at 6 months in the range of 31% [3]. Bevacizumab (BEV) has shown activity as determined by response and PFS in recurrent glioblastoma in uncontrolled phase II trials, leading to its registration in the US and other countries [4,5]. Despite concerns regarding the lack of durable responses and the failure to demonstrate of an overall survival (OS) benefit, the use of BEV in recurrent glioma has widely spread to other glioma entities. This may be due to beneficial effects of BEV on performance status and steroid use [6] and the apparent lack of alternative options after the failure of alkylating agent therapy.

The role of BEV alone or in combination with irinotecan in recurrent grade II and III gliomas has been less well studied than in glioblastoma, particular in Europe. We here report a retrospective analysis on the safety and efficacy of BEV alone or in combination with irinotecan in patients with recurrent grade II and III gliomas.

Patients and methods

We reviewed the reports of 39 unselected patients with grade II and grade III gliomas from 3 institutions (Heidelberg, Zurich, St. Gallen) who received BEV for progressive or recurrent

disease either as a single agent or in combination with irinotecan between 2007 and 2011. BEV was commonly administered at 10 mg/kg, and irinotecan at 125 mg/m^2 without use of enzyme-inducing antiepileptic drugs (EIAED) and at 340 mg/m^2 with use of EIAED, both at 2-weekly intervals. Radiological response to BEV-based therapy was formally re-evaluated using both Macdonald and RANO criteria [7,8] for this analysis at the sites without a *post-hoc* central review. Clinical benefit was defined by an improvement or stabilization of clinical symptoms, improvement of Karnofsky performance score (KPS) of 10 or more, or reduction of steroid use. The assessment of adverse events was restricted to the period of BEV therapy. Toxicity data were collected retrospectively using NCI common toxicity criteria (version 4.0). PFS and OS rates were calculated from the first dose of BEV until progression and death. Survival after progression under BEV was assessed from the date of progression until death. Progression and death did not occur before the arbitrarily chosen cut-off date of 1/10/2011 in 5 and 14 patients, respectively. These patients were censored at this cut-off-date. One patient lost follow-up before the cut-off date and was censored at the last date of MRI assessment. Data were analyzed by the Kaplan-Meier estimation method and statistical significance was determined by log-rank test (Mantel-cox) using the software of GraphPad Prism software version 5.0 (San Diego, CA, USA).

Results

Study population and pretreatment characteristics

Detailed patient characteristics are summarized in Table 1. Thirty-nine patients were identified: All patients had been pretreated with temozolomide and some patients also with nitrosourea-based chemotherapy. All but one had received radiotherapy. One patient with an extensive grade II glioma, previously treated with temozolomide, opted against radiotherapy.

The median number of relapses before the administration of BEV-based regimens was 3 in the monotherapy group and 4.5 in the combination group. It was 4 for grade II tumors and 3 for grade III tumors.

Treatment

27 patients, 14 with grade II and 13 with grade III glioma and a median KPS of 80 were treated with BEV alone, and 12 patients, 7 with grade II and 5 with grade III glioma and a median KPS of 90 received BEV in combination with irinotecan. The duration of BEV treatment was 3.6 months for monotherapy and 4.5 months with the combination (Table 2). Interruption of therapy for more than 4 weeks occurred in 6 of 39 patients because of patients` or physicians` decision.

Toxicity

Both BEV monotherapy and BEV in combination with irinotecan were generally well tolerated (Table 3). Arterial hypertension was a common adverse event with an overall incidence of 26% in the monotherapy and 33% in the combination group. Grade 4 leukopenia was observed in one patient only. No thromboembolic events or hemorrhages were reported.

Outcome

Some clinical benefit was noted in more than half of the patients (Table 2). A KPS increase of 10% was seen in 14.8% of patients with BEV alone and 8.3% of patients with BEV in combination. No patient had an increase in KPS of 20% or more. 26% of the patients in the BEV monotherapy and 33% in the combination group achieved a partial response (PR) as assessed by Macdonald and by RANO criteria (Table 2). The median duration of the best response was 3.9 months in the monotherapy and 3.5 months in the combination group.

The PFS was different in one patient when using RANO criteria instead of Macdonald criteria. It was progressive disease (PD) instead of stable disease (SD) because of a progressive FLAIR lesion. In this patient, PFS by RANO was considered to be valid by the site and entered into our database. The comparison of PFS and OS between BEV monotherapy and combination with irinotecan did not indicate major differences either for all patients pooled or separated by grade or histology (Figure 1, Table 2). For grade II and III tumors pooled, the median PFS was 4.2 months and the PFS rate at 6 months (PFS-6) was 29% for BEV alone. For the combination, median PFS was 4.7 months and PFS-6 was 42%. The median OS was 14.8 months and the OS at 12 months 44% for BEV alone and 8.1 months and 42% with BEV plus irinotecan. Data split by histology are provided in Table 2. Overall, median PFS was 4.2 months and PFS-6 32% for patients with grade II tumors and 4.9 months and 35% for patients with grade III tumors. OS was 9.9 months for grade II and 14.8 months for grade III tumors.

We further analyzed the outcome after progression under BEV to evaluate whether the discontinuation of BEV may have affected survival. Thirty-one patients were available for that analysis since those patients had PD under BEV until the indicated cut-off date. BEV was continued as a monotherapy or in any combination therapy in 15 patients while BEV was stopped in 16 patients. Up to failure, treatment duration with BEV was 16 weeks in those who continued as opposed to 15 weeks in those who did not. Median OS from PD under BEV was 55 weeks with BEV versus 8.5 weeks without BEV (p=0.0022) (Figure 2). Interestingly, only one patient out of 12 (8%) of the combination group continued a BEV-containing regimen in contrast to 14 out of 27 (52%) patients in the monotherapy group. This may indicate a less favorable toxicity profile in the combination group. The observation that BEV was more likely to be continued when administered as a single agent may be one explanation on the observed benefit on OS in the BEV monotherapy group.

Discussion

This retrospective study confirms and extends the current knowledge on the safety and efficacy of BEV-based therapy for progressive or recurrent gliomas of WHO grades II and III. Table 4 provides an overview about the current literature available on this topic. In line with previous data, BEV was well tolerated with hypertension as a known risk to take care of [9]. An increased toxicity with the addition of irinotecan did not become apparent in this small patient population. However, the toxicity data have to be interpreted with caution since retrospective studies tend to underestimate toxicity.

Based on the perception that BEV has mainly an effect on contrast-enhancing tumor, the activity of BEV in low-grade tumors may be limited. However, previous reports as well as our current study suggest at least moderate activity for BEV in recurrent grade II and grade III gliomas. This may be due to a high proportion of secondary malignant progression of the tumor. In our series, all but 1 patient had contrast-enhancing tumor prior to institution of BEV, and progression to a higher histological grading was common in patients undergoing second surgery. Patients with grade II tumors had a higher median number of treatments for relapse or progression than patients with grade III tumors prior to BEV (4 versus 3). This may explain the apparent lack of a difference in outcome from BEV by tumor grade in this series.

Response rates and data for PFS and OS (Table 2) are comparable with previously published results (Table 4). The retrospective nature of this study limits the reliability of our data on clinical benefit, but at least half of the patients appeared to have improved with BEV, albeit transiently. Chamberlain and colleagues reported retrospective data of patients with recurrent anaplastic astrocytoma (n=25) and anaplastic oligodendroglioma (n=22) treated with BEV as a single agent with a PFS-6 of 60% and 68% and a median OS of 9 and 8 months [10,11]. However, a prospective study evaluating BEV as a single agent in 31 patients with recurrent

anaplastic glioma did not meet the primary endpoint of a PFS-6 of 50% [12]. Desjardins and colleagues reported modest activity for the combination of BEV with irinotecan (n=33) with a PFS-6 of 55% and median OS of 15 months in a prospective phase II trial of recurrent anaplastic gliomas [13]. This compares favorably with data from two similar, but retrospective studies indicating PFS-6 rates of 39% for a mixed population of anaplastic glioma and glioblastoma [14] and 42% for grade II and grade III oliogodendroglioma [15]. Similarly, our retrospective data do not indicate an additional value of the combination therapy compared with BEV alone.

Response assessments in the discussed studies were based on Macdonald criteria [7]. Aware of possibly alternative patterns of progression during anti-angiogenic therapy especially regarding non-enhancing T2 and FLAIR tumor volume we additionally determined response rates using the new RANO criteria [8; 14]. In 1 of 39 patients, the use of the RANO criteria showed a different result. Thus, the introduction of these novel criteria may alter response assessment and result in a change in treatment only in a minority of patients. The use of BEV in malignant glioma is often continued beyond progression because ill-defined rebound phenomena are feared. However, there is little evidence supporting the perception that withdrawing BEV is worse than continuing the drug after it has failed. In a small retrospective study, there was no significant difference in survival of high-grade glioma patients after a BEV-free regimen compared to the continued use BEV (91 days vs. 116 days) [16]. Similarly, a recent meta-analysis of 4 phase II studies conducted in patients with recurrent grade III gliomas did not show a significant difference between BEV-containing or non-containing salvage therapies after BEV failure for OS [17]. Our retrospective analysis suggests a prolonged OS if BEV is continued beyond progression. However, the interpretation of these data is difficult because the probability of a preselection of this patient population is high. The decision of continuing or withdrawing BEV is likely to have been influenced by clinical

performance status, age, patients´ and physicians´ preferences. To address this question, a prospective trial design including randomization of patients will be necessary.

In conclusion, there is evidence that BEV has activity not only in recurrent glioblastoma but also in grade II and grade III glioma. The effect on OS remains uncertain. In recurrent grade II and grade III glioma, a prospective phase II randomized study evaluating the efficacy of BEV with or without temozolomide (TAVAREC, EORTC 26091, NCT01164189) has started accrual. This trial and further prospective and randomized trial data will be needed for a better evaluation of the role of BEV as a single agent and in combination with other agents in order to improve the limited therapeutic options for patients with recurrent gliomas failing radiotherapy and alkylating agent chemotherapy.

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Conflicts of interest

Katharina Seystahl and Thomas Hundsberger have received honoraria for advisory board participation from Roche (Basel, Switzerland), Caroline Happold has received honoraria for advisory board participation from Merck, Sharpe & Dohme (Whitehouse Station, New Jersey). Wolfgang Wick has received honoraria for advisory board participation and lecturing from Roche (Basel, Switzerland) and honoraria for lecturing and research support from Merck, Sharpe & Dohme (Whitehouse Station, New Jersey), Michael Weller has received research support and honoraria for advisory board participation and lecturing from Roche (Basel, Switzerland), Merck Serono (Darmstadt, Germany) and Merck, Sharpe & Dohme (Whitehouse Station, New Jersey). Benedikt Wiestler and Antje Wick have no conflicts of interest to declare

Table 1: Patient characteristics

	BEV monotherapy			**BEV plus irinotecan**		
Glioma grade	II	III	II + III	II	III	II + III
Number of patients	n=14	n=13	n=27	n=7	n=5	n=12
Histology, n [%]						
Astrocytic	10 [71%]	6 [46%]	16 [59%]	6 [86%]	3 [60%]	9 [75%]
Oligoastrocytic	2 [14%]	3 [23%]	5 [19%]	1 [14%]	2 [40%]	3 [25%]
Oligodendroglial	2 [14%]	4 [31%]	6 [22%]	0 [0%]	0 [0%]	0 [0%]
Median age, years [range]	32 [19-51]	43 [15-67]	38 [15-67]	25 [20-34]	38 [28-55]	29 [20-55]
Gender, n [%]						
M	9 [64%]	7 [54%]	16 [59%]	4 [57%]	4 [80%]	8 [67%]
F	5 [36%]	6 [46%]	11 [41%]	3 [43%]	1 [20%]	4 [33%]
Extent of surgery at diagnosis, n [%]						
Biopsy	8 [57%]	3 [23%]	11 [41%]	0 [0%]	1 [20%]	1 [8%]
Resection	6 [43%]	10 [77%]	16 [59%]	7 [100%]	4 [80%]	11 [92%]
Previous radiotherapy, n [%]	14 [100%]	13 [100%]	27 [100%]	6 [86%]	5 [100%]	11 [92%]
Previous chemotherapy, n [%]						
Temozolomide	14 [100%]	13 [100%]	27 [100%]	7 [100%]	5 [100%]	12 [100%]

Nitrosourea-based	11 [79%]	5 [38%]	16 [59%]	4 [57%]	4 [80%]	8 [67%]
Other	1 [7%]	0 [0%]	1 [4%]	1 [14%]	0 [0%]	1 [8%]
Surgery at relapse, n [%]	10 [71%]	4 [31%]	14 [52%]	7 [100%]	5 [100%]	12 [100%]
Prior to relapse treated with BEV, n [%]	2 [14%]	0 [0%]	1 [7%]	0 [0%]	2 [40%]	2 [17%]
Higher histological grading	9 [64%]	0 [0%]	10 [37%]	4 [57%]	1 [20%]	5 [42%]
Contrast-enhancing tumor prior to therapy with BEV, n [%]	14 [100%]	13 [100%]	27 [100%]	7 [100%]	4 [80%]	11 [92%]
Median time from diagnosis to start with BEV [months]	105	56	71	117	91	104
Median number of relapses prior to BEV [range]	4 [1-6]	2 [2-9]	3 [1-9]	5 [1-6]	4 [3-6]	4.5 [1-6]
Median KPS prior to BEV, % [range]	80 [50-100]	80 [50-100]	80 [50-100]	90 [70-100]	90 [70-90]	90 [70-100]

Table 2: Response assessment and outcome

	BEV monotherapy			**BEV plus irinotecan**		
Glioma grade	II	III	II + III	II	III	II + III
Number of patients	n=14	n=13	n=27	n=7	n=5	n=12
Duration of BEV [months]						
Median	3.7	3.6	3.6	3.9	7	4.5
Range	0.9-16.5	0.4-14.6	0.4-16.5	1.4-14	2.9-29	1.4-36.8
Best response, n [%]						
Macdonald [7]						
Partial response	3 [21%]	4 [31%]	7 [26%]	3 [43%]	1 [20%]	4 [33%]
Stable disease	6 [43%]	3 [23%]	9 [33%]	2 [29%]	4 [80%]	6 [50%]
Progressive disease	5 [36%]	6 [46%]	11 [41%]	2 [29%]	0 [0%]	2 [17%]
RANO [8]						
Partial response	3 [21%]	4 [31%]	7 [26%]	3 [43%]	1 [20%]	4 [33%]
Stable disease	6 [43%]	2 [15%]	8 [30%]	2 [29%]	4 [80%]	6 [50%]
Progressive disease	5 [36%]	7 [54%]	12 [44%]	2 [29%]	0 [0%]	2 [17%]
Median duration of best response [months]	4.8	2.6	3.9	3.0	4.1	3.5
Clinical benefit [%]	64%	62%	63%	43%	60%	50%
Median PFS [months]	4.2	3.3	4.2	3.8	8.1	4.7
PFS-6 [%]	33%	25%	29%	29%	60%	42%
Median OS [months]	14.4	7.4	14.8	8.1	18.5	8.1
OS-12 [%]	50%	40%	44%	29%	60%	42%

Table 3: Toxicity

Adverse events	**BEV monotherapy** n=27			**BEV plus irinotecan** n=12		
	CTC grade		Total	CTC grade		Total
	½	¾	n=27	½	¾	n=12
Nonhematologic						
Hypertension	6	1	7 [26%]	4	0	4 [33%]
Nausea	0	0	0 [0%]	1	0	1 [8%]
Anorexia	0	0	0 [0%]	1	0	1 [8%]
Allergy	1	0	1 [4%]	0	0	0 [0%]
Epistaxis	1	0	1 [4%]	0	0	0 [0%]
Infection	1	0	1 [4%]	0	0	0 [0%]
Hematologic						
Anemia	2	0	2 [7%]	0	0	0 [0%]
Thrombocytopenia	2	2	4 [15%]	2	0	2 [17%]
Leukopenia	4	1	5 [19%]	6	0	6 [50%]

Table 4: Retrospective series and prospective phase II studies in anaplastic gliomas treated with bevacizumab

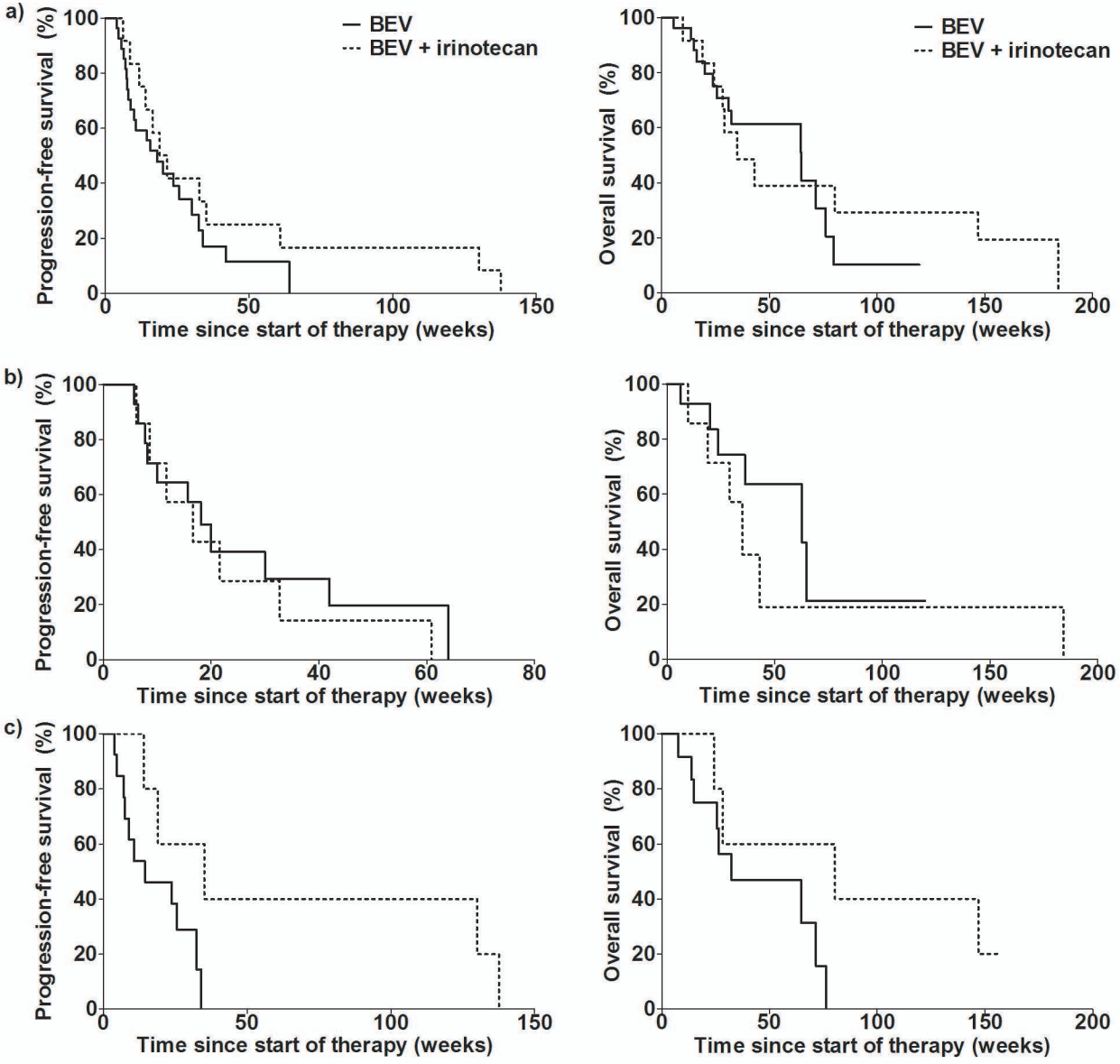
Reference	Trial design	Patients (diagnosis, n)	Regimen	Median PFS (months, 95% CI)	PFS-6	Median OS (months, 95% CI)
Chamberlain et al., 2008 [10]	Retrospective	Anaplastic astrocytoma, n=25	BEV monotherapy	7 (4.5-9.5)	60%	9.0 (6.6-11.4)
Chamberlain et al., 2008 [11]	Retrospective	Anaplastic oligodendroglioma, n=22	BEV monotherapy	8.0 (7.0-9.0)	68%	8.0 (6.3-9.7)
Kreisl et al. 2009 [12]	Phase II, single-arm, prospective	Anaplastic glioma, n=31	BEV monotherapy	2.9 (2.0-4.9)	20.9%	12 (6.1-22.8)
Norden et al, 2008 [14]	Retrospective	Anaplastic glioma n=21, glioblastoma n=33, High grade glioma n=1	BEV + irinotecan (85%), BEV + other chemotherapy (15%)	5.5 (4.1-6.5)	39%	8.2 (6.4-14.1)
Taillibert et al, 2009 [15]	Retrospective	Oligodendrogliomas grade II and grade III n=25	BEV+irinotecan	4.6 (3.9 - ∞)	42%	Not been reached
Desjardins et al., 2008 [13]	Phase II, single-arm, prospective	Anaplastic glioma, n=33	BEV + irinotecan	6.9 (4.8-13.8)	55%	14.9 (95% CI not indicated)
Reardon et al., 2009 [18]	Phase II, single-arm, prospective	Anaplastic glioma, n=32	BEV + etoposide	5.5 (3.7- 7.6)	41%	14.5 (8.3 - ∞)
Sathornsumetee et al., 2010 [19]	Phase II, single-arm, prospective	Anaplastic glioma, n=32	BEV + erlotinib	5.4 (4.2-8.3)	44%	16.4 (10.3-28.4)

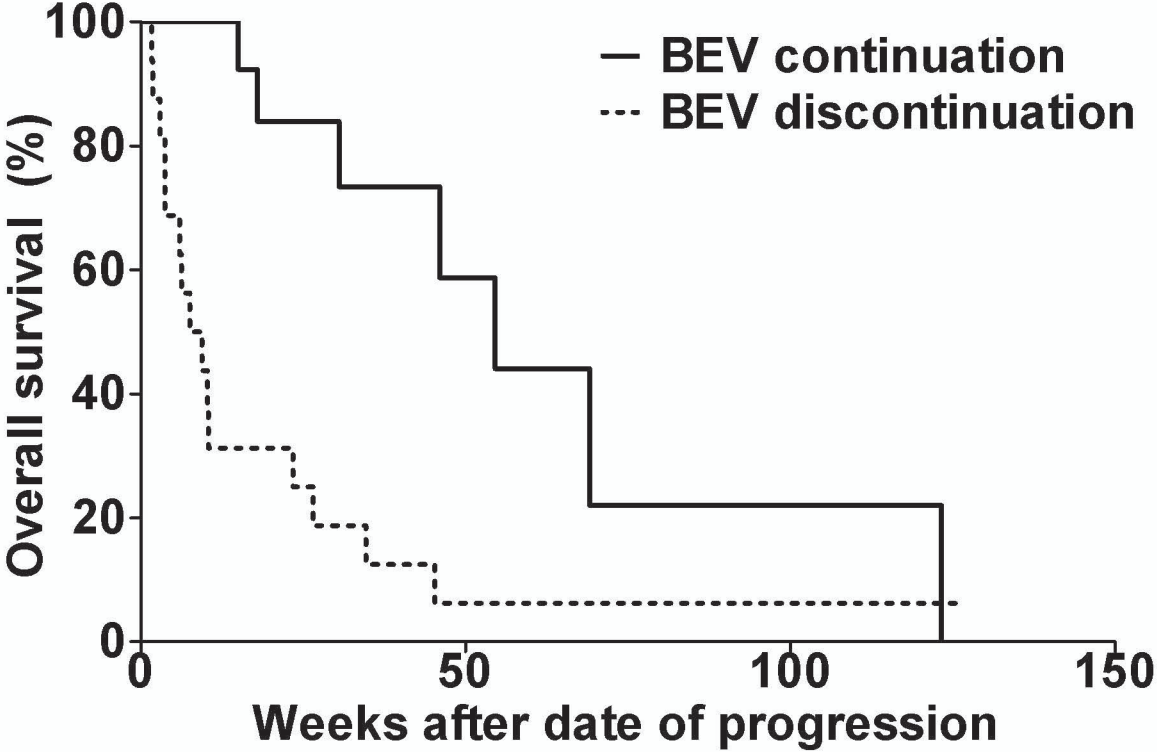
Figure 1: Progression-free and overall survival

Kaplan-Meier plots for PFS (left) and OS (right) for patients with grade II and grade III gliomas pooled (a), grade II gliomas only (b) or grade III gliomas only (c) receiving BEV alone (continuous line) or BEV plus irinotecan (dotted line).

Figure 2: Outcome after failure of the first BEV-containing regimen

Kaplan-Meier plot for OS after failure of the first BEV-containing regimen showing the proportion of patients continuing on a BEV-containing regimen (continuous line, n=15) *versus* patients discontinuing BEV (dotted line, n=16)


a)
Progression-free survival (%)
Time since start of therapy (weeks)
BEV
BEV + irinotecan
Overall survival (%)
Time since start of therapy (weeks)
BEV
BEV + irinotecan
b)
Progression-free survival (%)
Time since start of therapy (weeks)
Overall survival (%)
Time since start of therapy (weeks)
c)
Progression-free survival (%)
Time since start of therapy (weeks)
Overall survival (%)
Time since start of therapy (weeks)


100
80
60
40
20
0
Overall survival (%)
0
50
100
150
Weeks after date of progression
BEV continuation
BEV discontinuation